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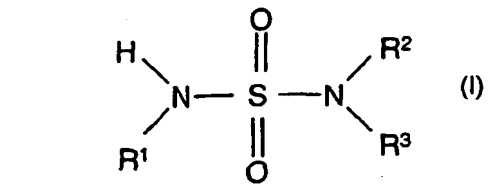
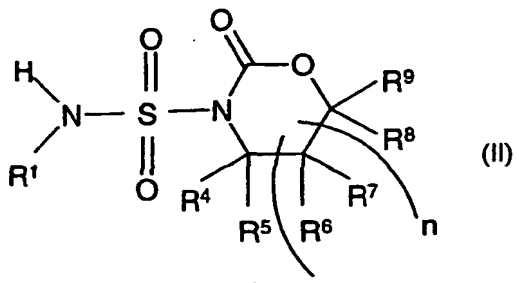
(54) Title: PROCESS FOR THE PREPARATION OF SULFAMIDES



(I)



(II)

(57) Abstract: A process for the production of an aryl sulfamide having formula (I), in which R^1, R^2 and R^3 are each hydrogen, alkyl, cycloalkyl or aryl, provided that at least one of R^1, R^2 and R_3 is aryl,which comprises reacting a compound of formula (II) where R^4, R^5, R^6, R^7, R^8 and R^9 are each hydrogen, alkyl or aryl, and n is 0 or 1, with an amine of the formula R^2R^3NH (III), in the presence of a strong base.

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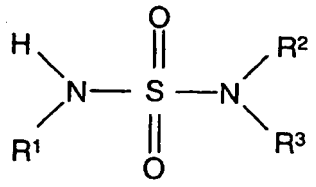
PROCESS FOR THE PREPARATION OF SULFAMIDES

This invention relates to a process for producing sulfamides, and to novel intermediates used in the process.

Sulfamides are conventionally prepared by the use of strongly electrophilic reagents such as sulfamoyl chloride, sulfonyl dichloride, phosphorus oxychloride or phosphorus pentachloride. Belgian patent 667.311 discloses a method of making sulfamides employing an N-alkyl sulfamoyl chloride. However, all such reagents involve aggressive synthetic methods, and indeed can be inconvenient or dangerous in their practical, industrial, application.

The invention provides a process for the production of aryl sulfamides that avoids the use of the above hazardous materials and conditions, and gives a high yield.

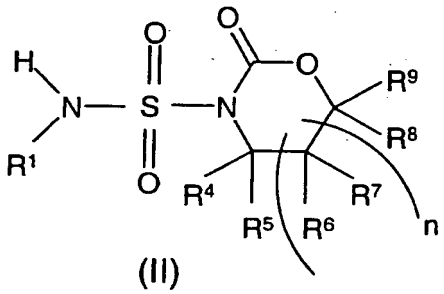
The process of the invention is for the production of an aryl sulfamide having the formula



(I)

in which R^1, R^2 and R^3 are each hydrogen, alkyl, cycloalkyl or aryl, provided that at least one of R^1, R^2 and R^3 is aryl,

which comprises reacting a compound of the formula



(II)

where R^4, R^5, R^6, R^7, R^8 and R^9 are each hydrogen, alkyl or aryl, and n is 0 or 1, with an amine of the formula R^2R^3NH (III), in the presence of a strong base.

The reaction can be carried out at ambient temperature or at the reflux temperature of the solvent in which the

reaction is performed, and generally the temperature of the reaction is chosen in the range of from 0• C. to 100• C. A polar, aprotic, solvent is preferred, as, for example, acetonitrile.

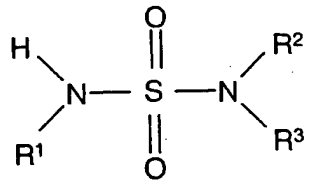
A strong base is required for the reaction to proceed, and examples include triethylamine, 1,8-diazabicyclo[5,4,0]undec-7-ene(DBU), 1,5-diazabicyclo[4,3,0]non-5-ene(DBN) or 1,4-diazabicyclo[2,2,2]octane(TED). Preferably from one to three equivalents of base are employed.

In the above formulae, an alkyl group can be substituted or unsubstituted, and is preferably C_{1-6} alkyl, being branched or unbranched. A cycloalkyl group preferably containing from 3 to 9 carbon atoms, and may, for example, be substituted by one to three alkyl groups such as methyl. When substituted, the alkyl group can be substituted by halo, C_{1-6} alkoxy, C_{3-9} cycloalkyl, optionally substituted phenyl or optionally substituted heteroaryl. An aryl group can be, for example, naphthyl or, preferably, phenyl, and can be substituted or unsubstituted. A substituted aryl group is substituted with one or more, preferably one to three, substituents

selected from, for example, an electron-donating substituent such as, for example, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, hydroxy, amino, or an electron-withdrawing substituent such as, for example, carboxy, nitro, cyano, trifluoromethyl, halo, C_{1-4} alkyl-SO- and C_{1-4} alkyl-SO_2-.

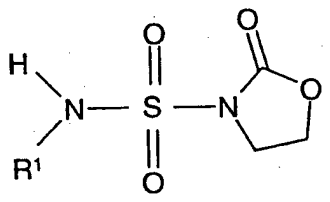
Preferably, R^1, R^2 and R^3 are selected from hydrogen, C_{1-6} alkyl and optionally substituted phenyl. In formula (II) above, R^4, R^5, R^6, R^7, R^8 and R^9 are preferably hydrogen, and n is preferably 0. It may, nevertheless, be desirable to employ a terminal moiety in which one or more of R^4 to R^9 is alkyl or aryl, for instance, in the preparation of stereoisomers.

It has been found that the nature of the substituent on an aryl group, for example a substituted phenyl, can surprisingly affect the reaction. Electron-donating substituents assist the reaction. Thus it is preferred that the substituent R^1 is optionally substituted alkyl or phenyl optionally substituted with an electron-donating substituent, and a preferred process is one for the preparation of a compound of the formula



in which R^1 is alkyl or phenyl optionally substituted with an electron-donating substituent, and R^2 and R^3 are each hydrogen, alkyl or optionally substituted phenyl, provided that R^1 is phenyl optionally substituted with an electron-donating substituent and/or R^2 is optionally substituted phenyl,

which comprises reacting a compound of the formula



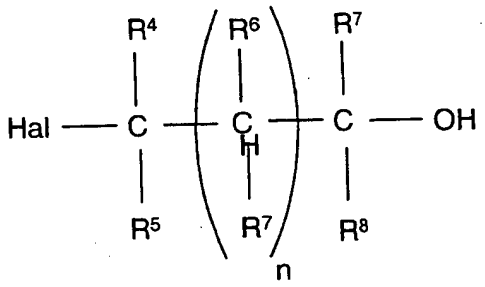
(IV)

with an amine of the formula R^2R^3NH, in the presence of a strong base. A particularly preferred process is one for the production of a compound of the above formula in

which R^1 is C_{1-6} alkyl or phenyl optionally substituted with an electron-donating substituent, R^2 is C_{1-6} alkyl or optionally substituted phenyl, and R^3 is hydrogen, provided that R^1 is phenyl optionally substituted with an electron-donating substituent and/or R^2 is optionally substituted phenyl.

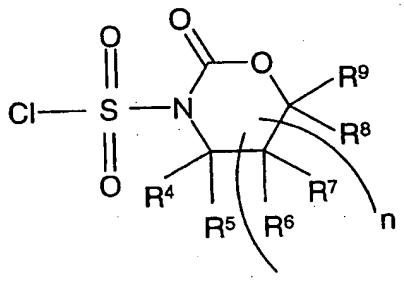
Compounds of formula (IV) where R^1 is phenyl optionally substituted with an electron-donating substituent are novel, with the exception of compounds in which R^1 is 3-methylbutyl or phenyl, and these novel compounds are included as an aspect of the present invention. They are stable, mainly crystalline solids, which can be readily isolated from the reaction medium.

Compounds of formula R^2R^3NH (III) employed in the above reactions are well known chemical compounds. As indicated above, some of the reactants of formula (II) are novel, but they can nevertheless be readily prepared by methods well known in the art. For example, compounds of formula (II) can be prepared by the reaction of chlorosulfonylisocyanate with an alcohol of formula



where Hal is chloro or bromo,

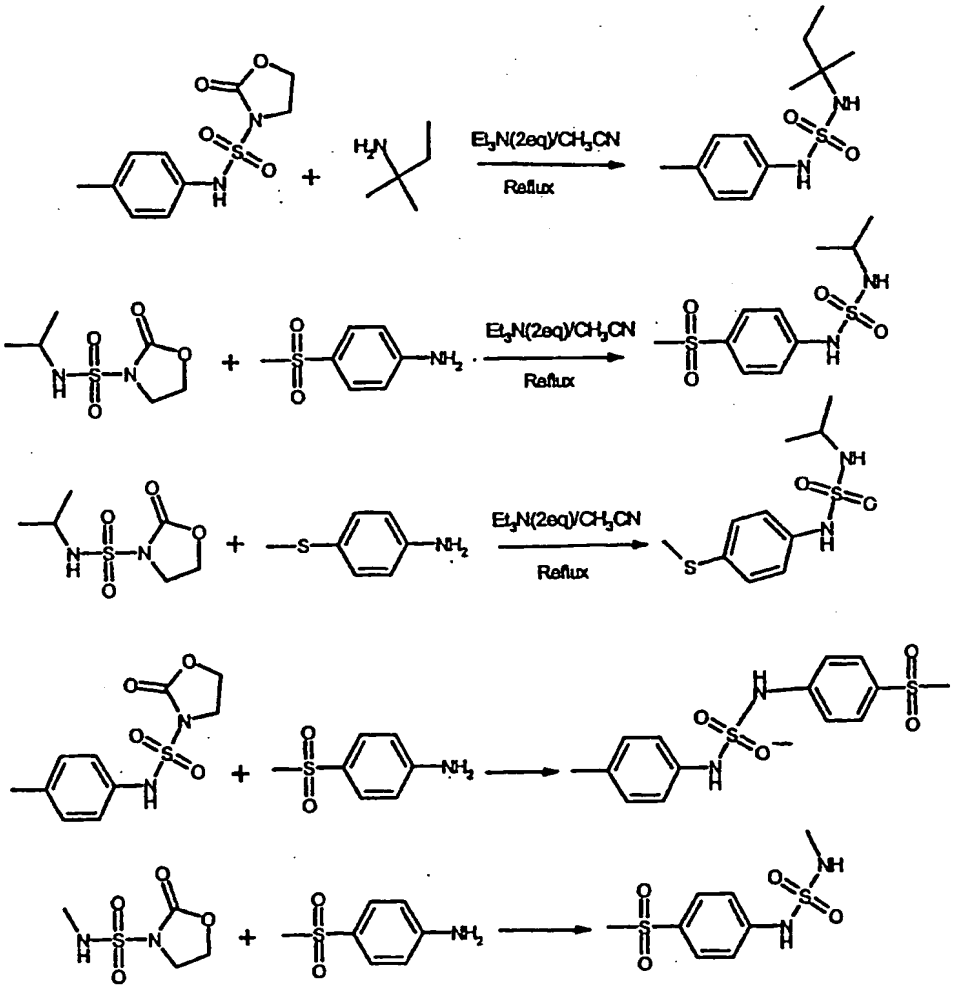
to give



which, in turn, when reacted with an amine of formula R^1NH_2, yields the desired compound of formula (II). The use of an appropriate optically pure alcohol can enable the production of diastereoisomers from which pure chiral sulfamides can be derived.

Examples of reactions according to the invention are as follows:

The sulfamides of formula (I) can be put to many uses. One such is disclosed in EP-A 0 897921, in which a sulfamide is cyclised to produce a benzothiadiazine dioxide intermediate employed in the preparation of pharmaceutically active compounds.



The following Examples illustrate the invention.

EXAMPLE 1

1,1-Dimethylpropylamino-1-sulfonic acid (4-methylphenyl)-amide

2-Oxo-oxazolidine-3-sulfonic acid (4-methylphenyl)-amide

To a 1 L reactor, charged with dichloromethane (176 ml) under an inert atmosphere (N_2) was added chlorosulfonyl isocyanate (CSI) (34.8 ml, 56.6 g, 0.40 mol) and the solution was cooled to 5 •C.

A solution of 2-bromoethanol(28.4 ml, 50.0 g, 0.40 mol, 1.0 equiv) in dichloromethane (176 ml) was added to the reaction mixture over 30 minutes under cooling to keep the temperature reaction mixture between 5-7 •C.

After stirring for about 30 minutes, a solution of p-toluidine (48.0 g, 0.45 mol, 1.1 equiv) and triethylamine (125 ml, 90.5 g, 0.90 mol, 2.2 equiv) in dichloromethane(358 ml) was added to the reaction

mixture over 30 minutes under cooling to keep the temperature reaction mixture around 5-7 •C.

After a stirring period of about 30 minutes 0.2N HCl (0.4 L) was added. Additional concentrated HCl (37% w/w) was added until the pH of the water layer was ±2. After decantation and separation of the aqueous layer, the organic layer was washed with 0.05 N HCl (0.4 L) and water (0.4 L).

To the washed and separated organic layer, water (0.4 L) was added followed by the removal of dichloromethane under vacuum. The resulting suspension was stirred for an additional 30 minutes.

The reaction mixture was filtered and the filter cake washed with water (0.2 L) and dried at 50 •C under reduced pressure to yield 90.82 g (0.355 mol) of crude 2-oxo-oxazolidine-3-sulfonic acid (4-methylphenyl)-amide.

Crude 2-oxo-oxazolidine-3-sulfonic acid (4-methylphenyl)-amide (50g) was suspended in dichloromethane (50 ml) and stirred for one hour at room

temperature. The suspension was filtered, washed with dichloromethane (40 ml) and dried under vacuum at 50 •C to yield pure 2-oxo-oxazolidine-3-sulfonic acid (4-methylphenyl)-amide (34.3 g). mp 159-160 •C.

1,1-Dimethylpropylamino-1-sulfonic acid (4-methylphenyl)-amide

Triethylamine (3.50 ml, 2.55 g, 25.2 mmol, 2.5 equiv) and *tert*-amylamine (1.50 ml, 1.12 g, 12.8 mmol, 1.3 equiv) were added to a solution of 2-oxo-oxazolidine-3-sulfonic acid (4-methylphenyl)-amide (2.56 g, 10 mmol, 1.0 equiv) in acetonitrile (12.5 ml). This mixture was heated at reflux for 8 h.

After cooling, water (40 ml) was added and the acetonitrile was removed by distillation under vacuum.

Dichloromethane (25 ml) was added to the resulting water emulsion and acidified with 1 ml HCl (37% w/w). After decantation and separation the organic layer was washed with 25 ml 0.05 N HCl and water (25 ml).

The organic layer was concentrated at room temperature under vacuum yielding the crude 1,1-Dimethylpropylamino-1-sulfonic acid (4-methylphenyl)-amide (1.802 g, 7.9 mmol) as a viscous yellow oil which slowly crystallised.

Crude 1,1-Dimethylpropylamino-1-sulfonic acid (4-methylphenyl)-amide (1.40 g, 6.13 mmol) was suspended in hexane (25 ml) and stirred at room temperature during 4 h.

The suspension was filtered, and the solid washed with hexane (10 ml). After drying the solid under vacuum at 50 •C, pure 1,1-Dimethylpropylamino-1-sulfonic acid (4-methylphenyl)-amide (609 mg, 2.67 mmol) was obtained. mp 92.5-93 •C.

EXAMPLE 2

4-Methylphenylylamino-1-sulfonic acid (4-methanesulfonylphenyl)-amide

Triethylamine (7.0 ml, 5.10 g, 50 mmol, 2.5 equiv) and 4-methanesulfonyl-phenylamine(4.28 g, 25 mmol, 1.25

equiv) were added to a solution of 2-oxo-oxazolidine-3-sulfonic acid (4-methylphenyl)-amide (5.12 g, 20 mmol) in acetonitrile (25 ml). This reaction mixture was heated at reflux for 8 hours.

After cooling, water (50 ml) was added and the acetonitrile was removed by distillation under vacuum.

To the obtained water emulsion were added dichloromethane (40 ml) and HCl (0.6 ml, 37% w/w). After decantation and separation of the aqueous layer, 0.05 N HCl (25 ml) was added to the organic layer. At this stage crystallisation occurred. Dichloromethane was removed by distillation under vacuum at room temperature.

The resulting suspension was filtered and the solid washed with water (40ml) and dichloromethane (1 ml). After drying under vacuum at 50 •C, 4-methylphenylamino-1-sulfonic acid (4-methanesulfonylphenyl)-amide (4.64 g, 13.6 mmol) was obtained, mp 165.5-167 •C.

EXAMPLE 3

1-Methylethylamino-1-sulfonic acid (4-methanesulfonylphenyl)-amide

2-Oxo-oxazolidine-3-sulfonic acid isopropyl-amide

To a 250 L glass lined reactor initially charged with dichloromethane (42 L) was added chlorosulfonyl isocyanate (4.5 kg, 31.8 mol) at room temperature and under a nitrogen atmosphere. The reaction mixture was cooled to about 1 •C. and a solution of 2-bromoethanol (4.00 kg, 1 equiv) in dichloromethane (14 L) was slowly added over 51 minutes in order to keep the reaction temperature between 0 and 10 •C. Stirring of the reaction mixture was continued at the same temperature for a minimum of 30 minutes. Progress of the reaction was monitored by ^{1}H-NMR. A mixture of isopropylamine (2.1 kg, 1.1 equiv) and triethylamine (7.1 kg) in dichloromethane (28 L) was then added at such an addition rate that the reaction temperature was maintained between 0 and 10 •C. The solution was heated up to room temperature. Aqueous hydrochloric acid (~0.2 N, 28.5 kg) was then added and the pH of the reaction mixture was adjusted to about 2 by addition of concentrated hydrochloric acid (450 ml in 2 portions).

The reaction mixture was decanted and the separated organic layer washed with aqueous hydrochloric acid (28.1 kg, ~0.05 N). The decanted and separated organic layer was washed with water (28 kg). To the decanted and separated organic layer, water (28 kg) was then added and the reactor was placed under vacuum to distil the maximum of dichloromethane while controlling the temperature below 25 •C. (84.4 kg of distillate). The resulting suspension was stirred for a minimum of 2 hours at room temperature, filtrated, rinsed twice wish water (2 x 7 L) and dried under vacuum at about 50 •C during 16 hours to afford the 2-oxo-oxazolidine-3-sulfonic acid isopropyl-amide, mp 107.5-108.5 •C.

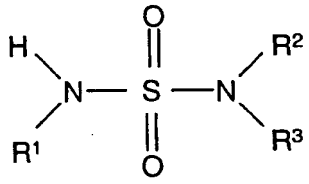
1-Methylethylamino-1-sulfonic acid (4-methanesulfonylphenyl)-amide

A 100 L glass lined reactor was charged with acetonitrile (17.8 kg) and 4-methylsulfonylaniline hydrochloride (3.36 kg, 16.2 mol) under stirring at room temperature. Triethylamine (4.5 kg) and 2-oxo-oxazolidine-3-sulfonic acid isopropyl-amide (3.70 kg,

1.1 equiv) were then added at the same temperature. The reaction mixture was heated to reflux and stirred at the same temperature for a minimum of 6 hours. The solution was then slowly cooled to room temperature and kept agitated over night. Water was slowly added over 40 minutes and the reactor was placed under vacuum to distil as much as possible of acetonitrile (27.8 kg of distillate) while maintaining the reaction temperature below 40 •C. The suspension was cooled to room temperature and stirred for a minimum of 2 hours before filtering the product. The cake was rinsed with water (16.2 kg) and dried under vacuum at about 50 •C. for a minimum of 16 hours to yield the 1-methylethylamino-1-sulfonic acid (4-methanesulfonylphenyl)-amide, mp 164-165 •C.

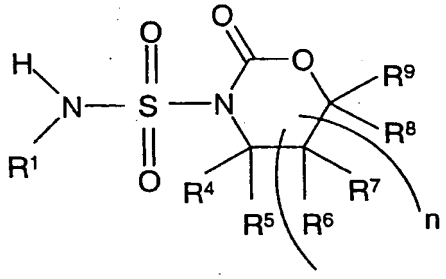
CLAIMS

1. A process for the production of an aryl sulfamide having the formula



in which R^1, R^2 and R^3 are each hydrogen, alkyl, cycloalkyl or aryl, provided that at least one of R^1, R^2 and R^3 is aryl,

which comprises reacting a compound of the formula

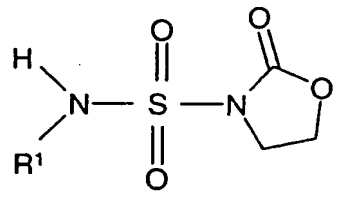


where R^4, R^5, R^6, R^7, R^8 and R^9 are each hydrogen, alkyl or aryl, and n is 0 or 1, with an amine of

the formula R^2R^3NH (III), in the presence of a strong base.

2. A process according to Claim 1 for the production of a compound in which R^1 is alkyl or phenyl optionally substituted with an electron-donating substituent, and R^2 and R^3 are each hydrogen, alkyl or optionally substituted phenyl, provided that R^1 is phenyl optionally substituted with an electron-donating substituent and/or R^2 is optionally substituted phenyl,

which comprises reacting a compound of the formula

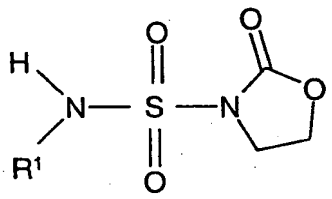


with an amine of the formula R^2R^3NH, in the presence of a strong base.

3. A process according to Claim 2 for the production of a compound in which R^1 is C_{1-6} alkyl or phenyl

optionally substituted with an electron-donating substituent, R^2 is C_{1-6} alkyl or optionally substituted phenyl, and R^3 is hydrogen, provided that R^1 is phenyl optionally substituted with an electron-donating substituent and/or R^2 is optionally substituted phenyl.

4. A compound of the formula



where R^1 is phenyl optionally substituted with an electron-donating substituent are novel, with the exception of compounds in which R^1 is 3-methylbutyl or phenyl.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/US 00/28877

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C303/34 C07D263/26 C07C307/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	G. DEWYNTER ET AL: TETRAHEDRON, vol. 52, no. 45, 1996, pages 14217-14224, XP004105028 page 14220, line 1 - page 14221, line 17; page 14221, experimental, typical procedures 2. ---	1,2
A	S.D. MCDERMOTT ET AL: SYNTHESIS, no. 3, 1983, pages 192-195, XP000978880 the whole document ---	1
A	B. AGOH ET AL: BULL. SOC. CHIM. FR., no. 5, 1987, pages 867-872, XP000978879 page 869, tableau 2, réf. 18 ---	4

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[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
23 January 2001	06/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Amsterdam, L

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INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/US 00/28877

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	M. ABDAOUI ET AL: TETRAHEDRON LETT., vol. 37, no. 32, 1996, pages 5695-5698, XP004030514 page 5697, table compound 1b	4

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